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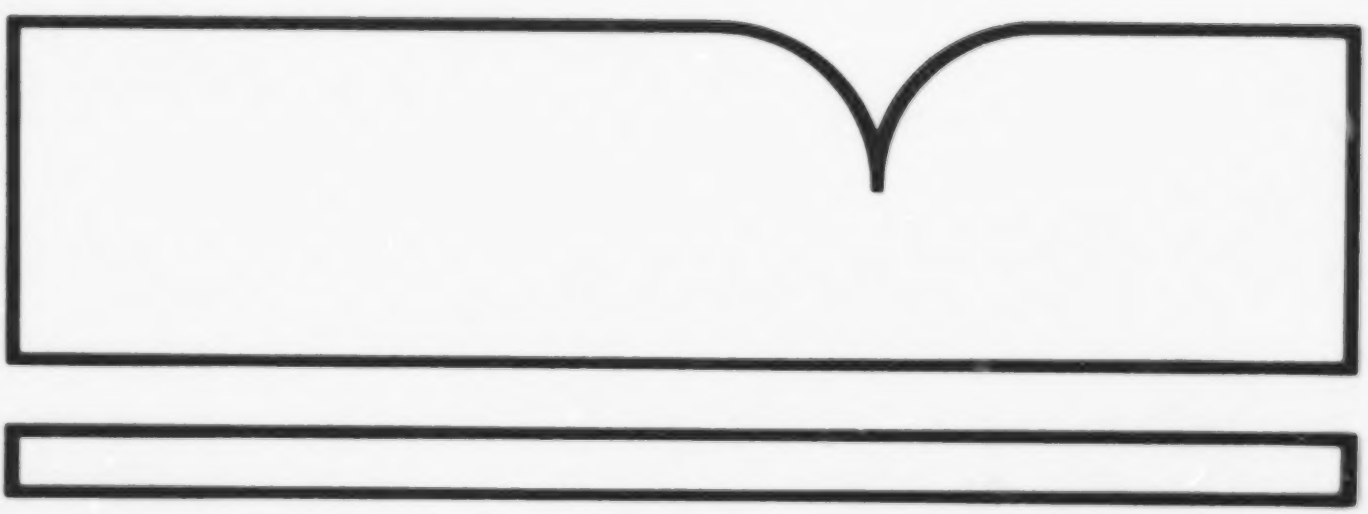

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EVALUATION OF REVERSE PHASE LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY FOR ESTIMATION OF N-OCTANOL/WATER PARTITION COEFFICIENTS FOR ORGANIC CHEMICALS

Lawrence P. Burkhard*

Center for Lake Superior Environmental Studies
University of Wisconsin-Superior
Superior, Wisconsin 54880

Douglas W. Kuehl and Gilman D. Veith

U.S. Environmental Protection Agency
Environmental Research Laboratory-Duluth
6201 Congdon Boulevard
Duluth, Minnesota 55804

ABSTRACT

A reverse-phase high pressure liquid chromatography/mass spectrometry (HPLC/MS) method was developed for estimating n-octanol/water partition coefficients (K_{ow}) of anthropogenic molecules in complex chemical mixtures (e.g., complex effluents and solid waste leachates). The average error for an estimated log K_{ow} was ca. 0.5 and this error was similar for both aliphatic and aromatic compounds. The minimum level of detection using the total ion current profile generally decreased with increasing molecular weight between 100 and 600 daltons. Results obtained demonstrate that the HPLC/MS method is a viable technique for estimating log K_{ow}'s of anthropogenic chemicals in complex environmental samples.

INTRODUCTION

The n-octanol/water partition coefficient (K_{ow}) is a useful chemical property for estimating the toxicological, pharmacokinetic, and physical-chemical properties of organic chemicals (1-6). These properties are not known for every chemical and consequently, are often estimated using structure-activity relationships based on the K_{ow}.

The data base for measured (experimental) K_{ow}'s is incomplete (5), especially for chemicals with high log K_{ow}'s (> 4.0). This lack of experimental data has occurred because measurement of the K_{ow} is time consuming and costly. Consequently, methods for estimating the K_{ow} have been developed.

Complex effluents and solid waste leachates are chemical wastes composed of many compounds. Prior to their disposal, a risk assessment should be performed to evaluate their potential to harm the environment and human health. This evaluation, hopefully, would enable safe handling and proper disposal of the waste.

To assess these mixtures, toxicological, pharmacokinetic, and physical-chemical properties are required for each chemical in the mixture. Subsequently, these properties are used in risk assessments models for evaluating each chemical and then for evaluating the joint toxic interaction of the entire chemical mixture. The key chemical property for performing this evaluation is the K_{ow}. With this property, nearly all of the other required properties can be estimated (2,7). Consequently, methods for quickly evaluating the K_{ow}'s of individual chemicals in chemical mixtures are required.

Methods for rapid estimation of K_{ow}'s using reverse-phase high pressure liquid chromatography (HPLC) have been developed (7-9). In these methods, retention volume of an organic chemical is proportional to K_{ow}. This method can estimate the K_{ow} of each component in a chemical mixture with one HPLC analysis.

The HPLC method using conventional detectors has two serious limitations, the inability to detect a wide variety of chemical classes, and/or lack of sensitivity. Consequently, the possibility exists that chemicals of concern could be missed because of inappropriate selectivity when analyzing uncharacterized chemical mixtures. The mass spectrometer (MS), however, is a universal detector not limited by these restrictions. In addition, the HPLC/MS method for estimating K_{ow}'s allows qualitative and possibly, quantitative analysis to be performed on an uncharacterized chemical mixture in the same HPLC analysis. This paper presents an evaluation of use of HPLC/MS for estimating K_{ow}'s of chemicals frequently encountered in environmental samples.

EXPERIMENTAL

Mass Spectrometer: A Finnigan-MAT 4500 quadrupole mass spectrometer (San Jose, CA) equipped with an INCOS data system was employed. The mass spectrometer was operated with electron impact (EI) ionization and with the following instrumental parameters: ion source temperature 150°C, electron energy 70 eV, emission current 250 ma, manifold temperature ca. 90°C, manifold pressure ca. 4.0×10^{-6} torr, scan range 50 to 550 daltons, total scan time 2.00s, and interscan time 0.05s.

LC/MS Interface: A modified Finnigan moving belt interface equipped with a Kapton polyimide belt was used. Modifications to the interface included the addition of vacuum gauges and foreline traps containing alumium oxide to the pumping system, replacement of the LC inlet system with a 11.5 mm x 0.12 mm ID dome-tipped needle (SGE, Austin, TX) placed at ca. 60° off vertical, the addition of a tension wheel between the drive and tension wheels for improved belt tracking, and the addition of a Balston exhaust filter (#AR-0335, Lexington, MA) to the large mechanical pump. Analysis conditions for the interface were: vaporizer and cleanup heaters 200°C, infrared heater 35%, belt speed 4.0 cm/sec, drive chamber vented to the atmosphere, first stage pressure > 100 torr, and second stage pressure 1.50 torr.

Chromatographic System: A Beckman 340 HPLC system (Berkeley, CA) consisting of a model 421 controller, model 160 absorbance detector and model 112 pumps was used. The

Beckman mixer/injection system was removed from the system and replaced with a modified injector to allow microbore chromatography. This system consisted of a stainless steel tee connecting the A and B effluent to 30 cm of 0.2 mm stainless steel tubing wound in a 2 cm ID coil and a 2μ stainless steel filtering frit which lead to an Altex model 210 injector. This system was found to provide adequate mixing of the A and B effluents for microbore work at flow rates as low as 50 μL/min. The Beckman 5 μL high resolution 254 nm ultraviolet detector was used to provide a UV monitor before MS analysis. Chromatography was performed on an Altex microbore column, 5.0 μm Ultrasphere-ODS 2.0 mm ID x 25 cm (Beckman, Berkeley, CA). Effluent from the HPLC detector flowed directly onto the Kapton belt through the dome-tipped needle.

Chemicals: Methanol, ethanol, and water (pH = 7.8) were HPLC grade (Waters Associated, Milford, MA), pure dehydrated (U.S. Industrial Chemicals, Tuscola, IL), and distilled water purified by UV photooxidation, respectively. Chemical standards were obtained from Aldrich Chemical (Milwaukee, WI), Chem Service (West Chester, PA), Analabs (North Haven, CT), Ultra Scientific (Hope, RI), and EPA Research Triangle Park Laboratory, and were used as received.

Method: The HPLC column was operated at ambient temperature and with a flow rate of 0.10 mL/min. The solvent conditions were isocratic for 1.0 minute initially with 100% solvent A, then linearly programmed to 100% solvent B at a rate of 6.67%/min, and then isocratic for 30 minutes with 100% solvent B. A 10.0 minute recycle time was allowed between runs with 100% solvent A. Solvents A and B were composed of methanol, ethanol, and water at compositions of 70.0:15.0:15.0 and 95.0:5.0:0.0. Ethanol was added to the solvents to aid in wetting the belt (12).

Seven chemicals with measured K_{ow}'s were used to correlate the elution time from the HPLC column to the K_{ow}'s. Compounds used were: chlorobenzene, 1,4-dichlorobenzene, 1,2,4-trichlorobenzene, 4,4'-dichlorobiphenyl, 2,2',4,5,5'-pentachlorobiphenyl, 2,2',3,3',5,5', 6,6'-octachlorobiphenyl, and decachlorobiphenyl and average log K_{ow} values selected from the literature were 2.62 (13,14), 3.38 (13,14), 4.08 (14,15), 5.42 (14,16,17), 6.18 (4,14,16), 7.12 (14,16) and 8.23 (14,16), respectively. For the chemicals with log K_{ow}'s of 6.00 or greater, their values were primarily determined using the "generator column" technique, a National Bureau of Standards method (18) and are the best values, currently available, for chemicals with high log K_{ow}'s.

The correlative relationship was found by regressing the logarithm of the K_{ow} against the logarithm of the corrected retention time (t_c) using an equation of the form:

$$\log K_{ow} = A * \log t_c + B$$

$$\text{where } t_c = t_r - t_o$$

where A and B are regression coefficients and t_r and t_o are the retention times for the solute of interest and for an unretained solute, respectively.

The retention time of the unretained solute was determined using acetone and acetonitrile. The correlative relationship was computed daily to eliminate small differences in retention due to temperature, minute variations in solvents, etc. The correlation coefficient was consistently greater than 92% and the average value for 29 different regressions was 97.0%. K_{ow}'s were estimated for each chemical using their experimental retention time and the correlative relationship. A typical correlative relationship is shown in Figure 1.

Chemical standards at concentrations ranging from 0.1 to 1.0 x 10^{-3} moles/L were used in determining the HPLC retention times. However, higher concentrations were used for chemicals with high volatility, with poor chromatographic peak shape, and/or with fragmentation patterns similar to the hydrocarbon background of the LC interface. All working and primary standard solutions used methanol as the solvent. The only exception was decachlorobiphenyl, and ca. 10% toluene (Burdick and Jackson, Muskegon, MI, pesticide grade) was added to the primary standard to aid in dissolving the compound.

RESULTS AND DISCUSSION

Log K_{ow}'s were estimated for 19 nonionizable chemicals with experimental values; an average error for the method is 0.52 (Table 1). This level of error has been observed in investigations using high performance liquid chromatography with ultraviolet detection (7,8). Similarity in estimation errors were expected since extracolumn band broadening in the moving belt interface is low (22). Plotting of the literature and HPLC estimated values (Figure 2) demonstrates no significant biases or trends in the predicted K_{ow}'s.

The HPLC/MS method was further evaluated by comparing the estimated values to those calculated using the CLOGP program of Leo (23) (Table 1). This comparison was performed because experimental log K_{ow}'s are limited for nonaromatic nonionizable compounds. However, this comparison must be viewed carefully since the CLOGP algorithm does have prediction deficiencies, e.g., calculated values of 7.00 or great may be unreliable (23). Consequently, the calculated values are only used for determining if gross deficiencies exist in the HPLC/MS K_{ow} estimates.

The average error between the estimated and calculated values was 0.70 overall and 0.53 for compounds with log K_{ow}'s less.than 7.00 (Table 1). These average errors are quite similar to the error observed between the estimated and literature values, 0.52 (Table 1) and to those observed using liquid chromatography with ultraviolet detection. In addition, the average error is similar for aromatic (0.81) and nonaromatic (0.62) compound classes. Plotting of the calculated and HPLC estimated values demonstrates that no gross biases in

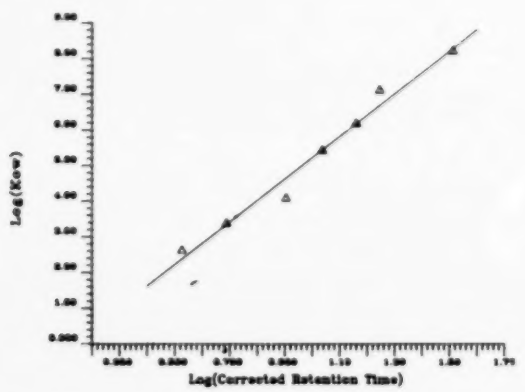

Figure 1. Log K_{ow} against log corrected retention time for calibration mixture.

Table 1. Comparison of Octanol/Water Partition Coefficients Estimated using HPLC/MS to Literature[a] and Calculated Values for Nonionizable Compounds.

Chemical	Log Kow			Absolute Deviation from Estimated Log Kow	
	Estimated	Lit	Cal	Lit	Cal
toluene	2.78	2.58	2.79	0.20	0.01
methyl heptanoate	3.10		2.79		0.31
1,2,3,4-tetrabromobutane	3.22		3.06		0.16
iodobenzene	3.23	3.25	3.26	0.02	0.03
p-chlorotoluene	3.46	3.32	3.50	0.14	0.04
2,5-dibromothiophene	4.15		3.64		0.51
1-bromohexane	4.58	3.80[b]	3.72	0.78	0.86
methyl nonanoate	4.62	4.32[b]	3.85	0.30	0.77
2,4,4-trimethyl-1-pentene	5.44		3.99		1.45
dipentene	5.70		4.23		1.47
diphenylether	3.79	4.26	4.24	0.47	0.45
diphenylmethane	4.22	4.14	4.36	0.08	0.14
methyl decanoate	4.62	4.41[b]	4.37	0.21	0.25
3[chloromethyl]heptane	5.20		4.51		0.69
2,2,4-trimethylpentane	5.83		4.54		1.29
phenothioxin	4.88		4.90		0.02
phenylcyclohexane	5.54	4.64[c]	4.91	0.90	0.63
pyrene	5.52	5.02[d]	4.95	0.50	0.57
9-methylanthracene	5.61	5.07[e]	5.14	0.54	0.47
methyl dodecanoate	6.02		5.43		0.59
1-bromodecane	6.35		5.84		0.51
n-decane	6.69		5.98		0.71
hexachlorobenzene	6.86	5.47[f]	6.42	1.39	0.44
methyl tetradecanoate	6.59		6.49		0.10
n-undecane	6.94		6.51		0.43
1,2:5,6-dibenzanthracene	6.88	6.50[g]	6.84	0.38	0.04
1-bromododecane	6.89		6.90		0.01
p,p'-DDT	5.44	4.98	6.91	0.46	1.47
p,p'-DDE	5.89	5.69	6.94	0.20	1.05
n-dodecane	7.24		7.04		0.20
methyl hexadecanoate	7.22		7.55		0.33
n-tetradecane	7.88		8.10		0.22
2,2',4,4',6,6'-hexachlorobiphenyl	6.39	7.55[f]	8.31	1.16	1.92
2,2',4,4',5,5'-hexachlorobiphenyl	6.68	6.65[h]	8.31	0.03	1.63
2,2',3,3',6,6'-hexachlorobiphenyl	5.48	6.81[i]	8.31	1.33	2.83
2,2',3,3',4,4'-hexachlorobiphenyl	6.28	6.98f	8.31	0.70	2.03
methyl octadecanoate	7.81		8.61		0.80
n-heptadecane	8.92		9.69		0.77
1-chlorooctadecane	8.70		9.93		1.23
Overall Absolute Deviations					
Mean				0.52	0.70
Standard Deviation				0.43	0.65
Number of Determinations				19	39

[a] Ref. 13 except when noted., [b] Ref. 19., [c] Ref. 20., [d] Average of Refs. 1, 13, 21., [e] Ref. 1., [f] Ref. 14., [g] Ref. 21., [h] Average of Refs. 1, 3, 16., [i] Ref. 16.

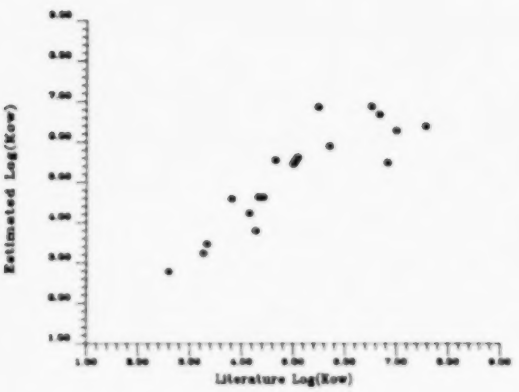

Figure 2. HPLC/MS estimated log K_{ow}'s vs. literature log K_{ow}'s for nonionizable compounds.

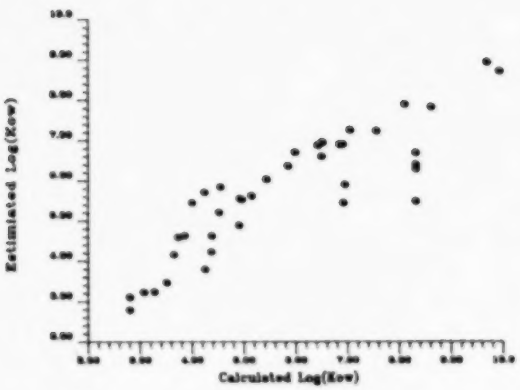

Figure 3. HPLC/MS estimated log K_{ow}'s vs. calculated log K_{ow}'s for nonionizable compounds.

Table 2. Comparison of Octanol/Water Partition Coefficients Estimated using HPLC/MS to Literature[a] and Calculated Values for Ionizable Compounds.

Chemical	Log D		Log Kow			Absolute Deviations from Estimated Log Kow			
	Est	pKa	Corrected	Lit	Cal	Log D Lit	Log D Cal	Corrected Lit	Corrected Cal
2,4,6-trimethyl-pyridine	3.48	6.69[b]	3.65		2.61		0.87		1.04
n-nonanol	3.31	16.20[c]	3.31	3.77[d]	3.47	0.46	0.16	0.46	0.16
n-nonanoic acid	3.36	4.96[e]	5.40		3.47		0.11		1.93
phenothiazine	2.49	5.58[c]	2.51		4.31		1.82		1.80
n-dodecanoic acid	5.37	4.80[c]	7.57	4.20	5.06	1.17	0.31	3.37	2.51
n-dodecanol	5.36	16.20[c]	5.36	5.13	5.06	0.23	0.30	0.23	0.30
2,6-ditertbutyl-4-methylphenol	5.20	12.55[c]	5.20		6.08		0.88		0.88
1-tetradecanol	6.03	16.20[c]	6.03		6.11		0.08		0.08
n-tetradecanoic acid	5.90	4.80[c]	8.10		6.11		0.21		1.99
n-hexadecanoic acid	6.52	4.80[c]	8.72		7.17		0.65		1.55
1-hexadecanol	6.65	16.20[c]	6.65		7.17		0.52		0.52
1-octadecanol	7.19	16.20[c]	7.19		8.23		1.04		1.04
n-octadecanoic acid	7.01	4.80[c]	9.21		8.23		1.22		0.98
1-eicosanol	7.75	16.20[c]	7.75		9.29		1.54		1.54
Overall Absolute Deviations									
Mean						0.62	0.69	1.35	1.17
Standard Deviation						0.49	0.56	0.75	1.75
Number of Determinations						3	14	3	14

[a] Ref. 13 except when noted., [b] Ref. 26., [c] Estimated (25)., [d] Ref. 19., [e] Ref. 24.

the estimated values exist (Figure 3). However, a slight disparity between the estimated and calculated values does occur for chemicals with large K_{OW}'s, i.e., where the calculated values may be unreliable.

The HPLC/MS method was also evaluated for ionizable compounds by estimating log distribution coefficients (log D) (27) for 14 chemicals (Table 2). Comparison of the literature and calculated (CLOGP) log K_{OW}'s to the estimated log D values reveals error levels which are similar to those for the nonionizable compounds (Table 1) and observed by others (7-9). Plotting of the log D values against the literature and calculated values (Figure 4) shows no significant biases or trends with increasing log D value.

Previous investigations (7,27-29) have reported that HPLC log D values for ionizable compounds are in better agreement with literature log K_{OW}'s after correction for ionization. Thus, log K_{OW}'s (Table 2) were calculated from the log D values using the method of Sherrer and Howard (27). In this investigation, agreement is worse between the HPLC/MS corrected values and the literature and calculated values after correction for ionization (Table 2). Currently, we can not explain this phenomenon. However, the corrections for ionization occur primarily for the carboxylic acids and cause the log K_{OW}'s to be much higher than the

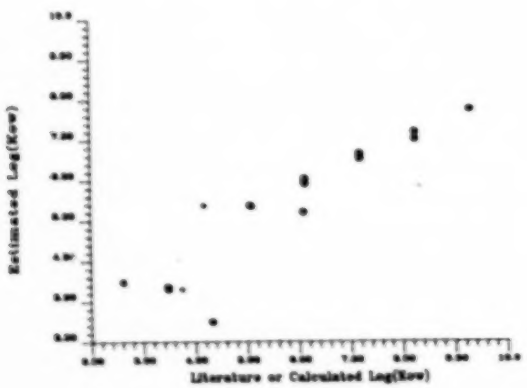

Figure 4. HPLC/MS estimated log K_{OW}'s vs. literature (star) and calculated (circle) log K_{OW}'s for ionizable compounds.

Table 3. Relative Molar Responses for 2.0 Nanomoles of the Seven Calibration Compounds.

	Relative Molar Response*	Molecular Weight	Boiling Point
	%	g	°C
Chlorobenzene	0.43	112.6	132
1,4-Dichlorobenzene	2.1	147.0	174
1,2,4-Trichlorobenzene	6.1	181.4	213.5
4,4'-Dichlorobiphenyl	78	223.1	315-9
2,2',4,5,5'-Pentachlorobiphenyl	100	326.4	344**
2,2',3,3',5,5'6,6'-Octachlorobiphenyl	105	429.8	394**
Decachlorobiphenyl	104	498.7	426**

* Pentachlorobiphenyl response = 100%. ** Estimated using the method of Meissner (2).

literature and calculated (CLOGP) values. This overcorrection suggests that the acids were unionized under the chromatographic conditions used. In fact, the water content in the solvent program is very low (0% for much of the program) and this would suppress the ionization of these compounds (30). Furthermore, examination of the log K_{OW}'s calculated using the CLOGP program reveals that n-alkane acids and alcohols with the same carbon number should be similar. Comparison of the log D values for n-alkane acid and alcohol pairs reveals similar values also. These results further suggest that the acids were unionized and that log K_{OW}'s instead of log D values were being estimated.

The above explanation appears plausible; however, other factors could account for this phenomenon. These include the use of estimated pKa values, the rather poor chromatographic behavior of the acids with unbuffered solutions, the influence of ethanol in the solvents, and hydrogen bonding between the acids and the octadecylsilica stationary phase.

Detection limits are an important consideration for the HPLC/MS method. Sensitivities for this method are dependent on a number of factors including the background created by the chromatographic solvents and the interface itself, losses due to volatilization from the belt during transport to the vaporizer head, chromatographic peak shape, the efficiency of vaporizing chemicals off of the belt and into the source, and ionization efficiency of the MS.

Numerous investigations have reported detection limits for the LC/MS interface used here (10,31). In general, 1 to 100 ng of a compound is required if full scan EI conditions are employed. In this investigation, 30 ng of the pentachlorobiphenyl yielded a signal to noise ratio of 2 for its base ion with full scan EI conditions. For the other calibration compounds, responses relative to the pentachlorobiphenyl were determined for 2.0 nanomoles of each compound (Table 3). These responses demonstrate that sensitivity increases with molecular weight and boiling point. The ionization processes for these chemicals are similar (32) and this would suggest that the observed differences in relative response are caused by losses of the compound in the interface. This trend of increasing sensitivity with increasing molecular weight was also observed for the n-alkanes, n-alcohols, etc. examined here. Consequently, we believe that the observed relative responses (Table 3) are fairly typical of most chemical classes.

As discussed by Hayes et al. (31), background from the interface can significantly influence sensitivity. In general, background from the interface itself is less at higher masses (> 150 daltons), and consequently, detection limits are slightly better for compounds with base peaks (or other large intensity ions) above 150 daltons. We observed this influence on sensitivity, also.

SUMMARY

A reverse-phase HPLC/MS method for estimating log K_{OW}'s was developed and evaluated. Comparison of literature and estimated values for 22 chemicals demonstrated that K_{OW} estimation using HPLC with mass spectrometry detection has similar predictive ability to that with ultraviolet detection. In addition, comparison of the estimated values to those calculated using the CLOGP program (23) for 53 chemicals revealed similar levels of error and further supports this conclusion. The average error for an estimated log K_{OW} was ca. 0.50 and this error was similar for aliphatic and aromatic compounds.

The sensitivity of the HPLC/MS method is quite good for higher molecular weight chemicals, e.g., 1 to 100 ng, and less for lower molecular weight chemicals (Table 3). This general trend in sensitivity is believed to be typical of most chemical classes. Furthermore, higher log K_{ow} chemicals tend to have high molecular weights and consequently, the chance of not detecting or missing a high log K_{ow} chemical (chemicals of concern) is low.

The correlative relationship used here has a much wider range (2.62 to 8.23) of log K_{ow}'s than that in current use (2.13 to 6.11) (7). Figure 1 and the observed errors (Tables 1 and 2) demonstrate that this set of standard compounds is satisfactory for the HPLC estimation method.

The intended use of the HPLC/MS method is for rapid analysis of complex chemical mixtures frequently encountered in the characterization of environmental samples for anthropogenic chemicals. The result presented here demonstrate that HPLC/MS can provide not only qualitative data traditionally obtained from modern mass spectrometry systems, but also an estimate of K_{ow}, an extremely important parameter used for hazard assessment. Furthermore, recent developments in HPLC/MS instrumentation, such as high resolution capillary liquid chromatography columns, and direct HPLC/MS interfacing techniques including Direct Liquid Introduction (DLI) and thermospray will greatly extend the usefulness of HPLC/MS for environmental analysis.

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